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Impact of diabetes mellitus on right ventricular dysfunction and ventricular interdependence in hypertensive patients with heart failure with reduced ejection fraction assessed via 3.0 T cardiac MRI

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Abstract

Background Hypertension (HTN) and diabetes mellitus (DM) are two common comorbidities of heart failure with reduced ejection fraction (HFrEF), each of which can cause right ventricular (RV) dysfunction. The aim of this study was to investigate the impact of DM on RV dysfunction and ventricular interdependence in hypertensive HFrEF patients via cardiac magnetic resonance imaging (MRI) feature tracking.

Methods This study included 249 patients with HFrEF: 77 HFrEF controls, 97 with hypertensive HFrEF (HTN-HFrEF [DM-]) and 75 with hypertensive HFrEF and comorbid DM (HTN-HFrEF [DM+]). The cardiac MRI-derived biventricular global radial (GRS), circumferential (GCS) and longitudinal (GLS) peak strains were obtained and compared among the groups. Multivariable linear regression and mediation analyses were used to evaluate the effects of DM and left ventricular (LV) strain on RV strain.

Results The biventricular GLS and GLS of segments 8, 9 and 14 of the interventricular septum (IVS) decreased gradually from the HFrEF control group to the HTN-HFrEF (DM–) group to the HTN-HFrEF (DM+) group (all $P < 0.05$). Patients with DM had even lower biventricular GCS and IVS strains in all directions in specific segments than did those without DM and the HFrEF controls (all $P < 0.05$). DM was independently associated with impaired RVGLS and RVGCS (both $P < 0.05$) in hypertensive HFrEF patients. The difference in RVGLS between the hypertensive HFrEF subgroups was partly mediated by LVGLS [β = 0.80, 95% CI (0.39–1.31)], and that of RVGCS was partly mediated by LVGCS [β = 0.28, 95% CI (0.01–0.62)].

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Conclusions In hypertensive HFrEF patients, comorbid DM may have aggravated RV dysfunction and was an independent determinant of impaired RV strain. RV dysfunction might be directly affected by DM and partially mediated by LV strain through unfavorable ventricular independence.

Keywords Diabetes mellitus, Hypertension, Heart failure with reduced ejection fraction, Ventricular interdependence, Right ventricle strain

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a progressive clinical syndrome accounting for approximately 50% of general HF cases [1]. HFrEF has a high burden of mortality and hospitalization, and beneficial guideline-directed medical therapy is vastly underutilized in real-world clinical practice [2]. Hypertension (HTN) is a leading risk factor for HF and other cardiovascular diseases and is highly prevalent among patients with HFrEF [3]. HTN further promotes myocardial hypertrophy and remodeling, which are associated with poor clinical outcomes [4]. HTN and diabetes mellitus (DM) are the main comorbidities of HFrEF, and they often coexist due to shared risk factors [5, 6]. Coexisting DM further promotes HFrEF progression and is associated with adverse outcomes [7]; thus, HFrEF patients with comorbid HTN and DM may need additional surveillance and more personalized treatment.

In the advanced stages of HFrEF, right ventricular (RV) dysfunction occurs and has an important impact on disease progression, morbidity and mortality [8, 9]. However, studies on HFrEF patients with concomitant HTN and DM have focused mainly on the left ventricle (LV) [4, 10, 11]. RV function may not only contribute to risk stratification but also complicate treatment in HFrEF patients [12, 13], and RV strain parameters offer increased prognostic value to LVEF in HFrEF patients [14]. Therefore, early and simultaneous evaluation of RV function in HFrEF patients is highly clinically important. HTN and DM can each cause RV dysfunction separately, and RV impairment may be a consequence of ventricular interdependence [15–17]. However, the synergistic effects of DM on RV function and the biventricular interaction in hypertensive HFrEF patients remain unexplored. Cardiac magnetic resonance imaging (MRI) feature tracking significantly improves RV functional assessment [18]. Considering all these factors, the aim of the present study is to evaluate the effects of DM on RV systolic function in hypertensive HFrEF patients and investigate the mediating effects of LV dysfunction on RV strain in these patients via cardiac MRI feature tracking.

Materials and methods

Study population

This study was approved by the Biomedical Research Ethics Committee of our hospital, and written informed consent was waived because of the retrospective nature of the study. From October 2017 to March 2024, we retrospectively enrolled consecutive patients who were clinically diagnosed with concomitant HFrEF and HTN. According to the guidelines of the European Society of Cardiology (2021) [1], patients who had a reduced LVEF (≤40%) with symptoms and/or signs of HF and an elevated level of animo-terminal pro-B-type natriuretic peptide (NT-proBNP) were diagnosed with HFrEF. A history of HTN was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg [19] in the clinic. The above enrolled patients were further divided into two groups, the HTN-HFrEF (DM-) and HTN-HFrEF (DM+) groups, on the basis of the current DM status definition from the European Society of Cardiology (2019) [20]. HFrEF patients with a history of neither HTN nor DM during the same period were included in the HFrEF control group. The exclusion criteria were (1) idiopathic pulmonary artery HTN, (2) secondary HTN, (3) severe arrhythmia or severe valve disease, (4) congenital heart disease, (5) acute coronary syndrome or an ischemic etiology with ventricular aneurysm formation, (6) pericardial disease, or (7) incomplete clinical records or poor cardiac MRI image quality. All patients were followed for the primary composite outcomes of HF readmission, all-cause mortality and heart transplantation through data from electronic medical records or phone calls to patients or family members. Follow-up duration was calculated as the time from cardiac MRI to the occurrence of any endpoint or the date of the last follow-up (August 2024).

Cardiac MRI protocol

Cardiac MRI was performed on a 3-Tesla scanner (MAGNETOM Skyra/Tim Trio; Siemens Healthcare, Erlangen, Germany). Balanced steady-state free precession cine images were acquired with a retrospective segmented ECG gating technique at the end-expiratory breath-hold, with twenty-five frames reconstructed per breath-hold acquisition. Standard short-axis, two- and four-chamber long-axis view cine images covering the entire left and right ventricles were acquired. The scanning parameters were as follows: repetition time = 2.81 ms; echo time = 1.22 ms; flip angle = 40°/50°; slice thickness = 8.0 mm; acquisition matrix = 256 × 166/208 × 139 pixels; and field of view = 340 × 285/250 × 300 mm^2.

Cardiac MRI analysis

The cardiac MRI cine images were uploaded to the offline commercial software CVI[42] (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) and analyzed by two radiologists (G.Z. and K.S.) with more than 3 years of cardiac MRI experience who were blinded to the clinical data of the subjects. The interobserver variabilities of the RV (0.798–0.891) and LV (0.835–0.918) strain measurements as shown by intraclass correlation coefficients (ICCs) were excellent.

To calculate the biventricular volumetric and functional parameters, including the LV and RV end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), EF and myocardial mass (M), the endo- and epicardial contours of both ventricles were semiautomatically delineated and manually corrected at the ED and ES phases in a series of short-axis images. The papillary muscle and trabeculae were included in the ventricular volume analyses but excluded from the myocardial M analysis. The LV/RV EDV, LV/RV ESV, LV/RV SV, and LV/RV M were standardized by body surface area (BSA). The LV and RV remodeling indices were calculated as the LVM/LVEDV and RVM/RVEDV, respectively.

For biventricular feature tracking analyses, the endo- and epicardial contours of both ventricles in the additional LV two- and four-chamber long-axis views and RV four-chamber long-axis views were tracked at end diastole (reference phase). The RV (Fig. 1) and LV global radial (GRS), circumferential (GCS) and longitudinal (GLS) peak strains and the LV segmental strains were generated automatically. According to the AHA 16-segment model, the 2, 3, 8, 9 and 14 LV segments represented the area of the interventricular septum (IVS) [16].

Statistical analysis

Continuous data are presented as the mean±standard deviation (SD) or median (interquartile range, IQR), depending on the results of the normality evaluation by the Kolmogorov–Smirnov test. Categorical data are expressed as frequencies (percentages) and were compared via the chi-square test or Fisher's exact test. The baseline characteristics and cardiac MRI-derived parameters were compared by one-way analysis of variance followed by Bonferroni's post hoc correction or the Kruskal–Wallis test, as appropriate. Pearson's correlation coefficients were calculated to analyze the correlations between cardiac MRI-derived RV, LV and IVS parameters. Multivariable linear regression analysis was used to identify the determinants of impaired RV strains, and candidate variables with a P value<0.05 in the univariable analysis and traditional clinical risk factors were added to the stepwise backward multivariable linear regression models. Bootstrap mediation analyses [21] were performed to assess ventricular interdependence on the differences in RV strains in hypertensive HFrEF patients. Kaplan-Meier survival analysis with a log-rank test was used to assess the long-term adverse outcomes among groups. A two-tailed P value<0.05 was considered to indicate statistical significance. The statistical analyses were performed via SPSS statistical software (version 27.0; SPSS Inc., Chicago, IL, USA) and R software, version 4.4.0 (The R Foundation, Vienna, Austria).

Results

Baseline characteristics

The current study included 249 participants, including 77 HFrEF control patients, 97 HTN-HFrEF (DM-) patients, and 75 HTN-HFrEF (DM+) patients. The detailed baseline characteristics of the study population are shown in Table 1. The three groups did not differ in terms of sex, heart rate, HF duration or HTN duration (all $P>0.05$). Patients in the two hypertensive HFrEF subgroups had higher body mass index (BMI) ($P=0.006$), mean SBP, mean DBP and mean pulse pressure (PP) (all $P<0.001$). Compared with those in the HFrEF control group, the patients in the HTN-HFrEF (DM+) group were older ($P=0.003$) and had a higher median NT-proBNP level ($P=0.001$) but a lower mean estimated glomerular filtration rate (eGFR) ($P<0.001$).

HTN-HFrEF (DM+) patients had the highest levels of fasting blood glucose and glycated hemoglobin (HbA1c) among the groups (both $P<0.001$). With respect

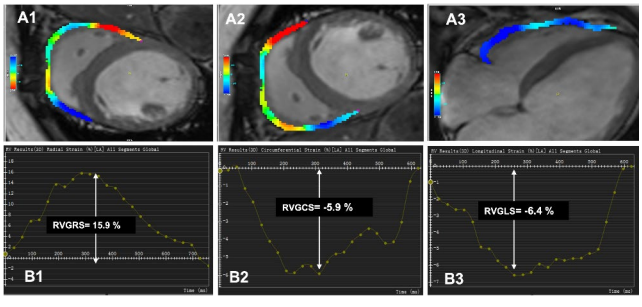

Fig. 1 Representative cardiac MRI color-coded strain (A1: radial, A2: circumferential, A3: longitudinal) images of the right ventricle in the short-axis two-chamber and long-axis four-chamber views at the end-systole and cardiac MRI-derived global radial (B1), circumferential (B2) and longitudinal (B3) strain–time curves of a hypertensive HFrEF patient with comorbid DM

Table 1 Baseline characteristics of the study population

	HFrEF controls *n* = 77	HTN-HFrEF (DM-) *n* = 97	HTN-HFrEF (DM+) *n* = 75	*P* value
Age, yrs	48.9 ± 13.3	52.7 ± 16.0	56.7 ± 11.8*	0.004
Male, n (%)	50 (64.9)	73 (75.3)	55 (73.3)	0.298
BMI, Kg/m^2	23.7 ± 4.0	25.7 ± 5.3*	25.9 ± 4.3*	0.006
Heart rate, bpm	81.4 ± 17.2	85.1 ± 18.1	85.7 ± 16.9	0.252
SBP, mmHg	109.3 ± 15.9	133.0 ± 18.9*	129.0 ± 20.3*	< 0.001
DBP, mmHg	71.7 ± 12.9	87.6 ± 17.5*	83.0 ± 17.2*	< 0.001
PP, mmHg	37.6 ± 12.2	45.4 ± 14.6*	46.0 ± 15.1*	< 0.001
HF duration				0.316
≤ 1 yr	45 (58.4)	66 (68.0)	44 (58.7)	
>1 and<5 yrs	26 (33.8)	22 (22.7)	20 (26.7)	
≥ 5 yrs	6 (7.8)	9 (9.3)	11 (14.7)	
NYHA functional class ≥ III, n(%)	42 (54.5)	58 (59.8)	50 (66.7)	0.310
HTN duration				0.721
≤ 1 yr		20 (20.6)	14 ((18.7)	
>1 and<5 yrs		26 (26.8)	16 (22.7)	
≥ 5 yrs		51 (52.6)	43 (58.7)	
Cardiovascular risk factors, n (%)				
Smoking	30 (39.0)	42 (42.3)	34 (45.3)	0.729
Dyslipidemia	22 (28.6)	41 (42.3)	30 (40.0)	0.152
AF	5 (6.5)	9 (9.3)	16 (21.3)*	0.011
CAD	17 (22.1)	32 (33.0)	37 (49.3)*	0.002
Laboratory data				
NT-proBNP, pg/ml	1119 (593–3853)	1733 (849–4187)	2785 (1362–7335)*	< 0.001
TG, mmol/L	1.3 (1.0–2.0)	1.6 (1.0–2.3)	1.5 (1.1–2.2)	0.174
TC, mmol/L	4.1 (3.2–4.9)	4.2 (3.5–4.9)	3.9 (3.3–4.8)	0.424
HDL, mmol/L	1.2 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	0.180
LDL, mmol/L	2.5 ± 1.0	2.6 ± 0.8	2.4 ± 1.0	0.404
Fasting blood glucose, mmol/L	5.5 (4.7–6.6)	5.7 (5.1–6.6)	7.5 (6.2–10.8)*§	< 0.001
HbA1c (%)	5.7 ± 0.4	6.0 ± 0.5	7.5 ± 1.5*§	< 0.001
eGFR, mL/min/1.73 m^2	85.3 ± 27.4	75.9 ± 24.0	69.5 ± 26.2*	0.001
Medications, n (%)				
Beta-blocker	57 (74.0)	73 (75.3)	62 (82.7)	0.384
CCB	1 (1.3)	22 (22.7)*	15 (20.0)*	< 0.001
ACEI/ARB	66 (85.7)	81 (83.5)	64 (85.3)	0.909
Anti-thrombotic agents	29 (37.7)	42 (43.3)	43 (57.3)*	0.042
Any diuretics	62 (80.5)	73 (75.3)	53 (70.7)	0.368
MRA	45 (58.4)	70 (72.2)	51 (68.0)	0.155
Statins	27 (35.1)	47 (48.5)	40 (53.3)	0.062
Digoxin	21 (12.6)	21 (21.6)	17 (22.1)	0.200

The data are presented as the means ± SDs, medians (Q1–Q3) or numbers (percentages)

HFrEF: heart failure with reduced ejection fraction; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; HF: heart failure; NYHA: New York Heart Association; AF: atrial fibrillation; CAD: coronary artery disease; NT-proBNP: amino-terminal pro-B-type natriuretic peptide; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; CCB: calcium-channel blocker; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist

*P less than 0.05 vs. HFrEF controls

§P less than 0.05 vs. HTN-HFrEF (DM–) group

to cardiovascular risk factors, atrial fibrillation (AF) (P=0.008) and CAD (P<0.001) were more prevalent in the HTN-HFrEF (DM+) group than in the HFrEF control group. The use of cardiovascular medications was similar among the three groups, except that antithrombotic agents were used more often in the HTN-HFrEF (DM+) group than in the HFrEF control group (P=0.015), and calcium channel blockers were used least often in the HFrEF control group (P<0.001).

Comparison of biventricular functional parameters

Patients in the HTN-HFrEF (DM-) and HTN-HFrEF (DM+) groups had higher LVMI [82.0 (70.5–93.6) g/m^2 vs. 82.2 (68.6–95.9) g/m^2 vs. 67.6 (56.1–79.6) g/m^2, P<0.001] and LVRI [0.53 (0.47–0.67) g/mL vs. 0.58 (0.45–0.76) g/mL vs. 0.44 (0.40–0.54) g/mL, P<0.001] than those in the HFrEF control group (Table 2). No differences were found in the LVEF, LVEDVI, LVESVI, or LVSVI among the three groups (all P>0.05). Compared with those in the HFrEF control group, patients in the HTN-HFrEF (DM+) group had lower RVEF (36.5 ± 14.5% vs. 44.9 ± 13.3%, P=0.002) and a higher RVMI [19.6 (16.1–24.7) g/m^2 vs. 17.2 (14.5–21.4) g/m^2, P=0.039], RVESVI (46.0 ± 28.5 mL/m^2 vs. 34.9 ± 17.2 mL/m^2, P=0.013), and RVSVI (22.9 ± 8.4 mL/m^2 vs. 26.5 ± 9.2 mL/m^2, P=0.042). There were no significant differences in the RVRI (P=0.081) or RVEDVI (P=0.079) among the three groups.

Comparison of global biventricular and IVS strain parameters

The RV (-9.9 ± 3.5% vs. -8.6 ± 3.7% vs. -6.3 ± 2.8%, P<0.001) and LV (-6.9 ± 2.1% vs. -5.7 ± 2.2% vs. -4.1 ± 1.4%, P<0.001) GLS decreased gradually from the HFrEF control group to the HTN-HFrEF (DM–) group to the HTN-HFrEF (DM+) group. The patients in the HTN-HFrEF (DM+) group had the lowest RV (-9.3 ± 4.3% vs.

Table 2 Comparison of LV and RV functional parameters

	HFrEF controls *n* = 77	HTN-HFrEF (DM-) *n* = 97	HTN-HFrEF (DM+) *n* = 75	*P* value
LV parameters				
LVEF, %	27.2 ± 6.8	27.1 ± 7.5	25.1 ± 8.2	0.157
LVMI, g/m^2	67.6 (56.1–79.6)	82.0 (70.5–93.6)*	82.2 (68.6–95.9)*	< 0.001
LVRI, g/mL	0.44 (0.40–0.54)	0.53 (0.47–0.67)*	0.58 (0.45–0.76)*	< 0.001
LVEDVI, mL/m^2	154.1 ± 50.1	159.4 ± 53.4	154.7 ± 52.4	0.763
LVESVI, mL/m^2	112.4 ± 38.7	117.8 ± 47.1	117.8 ± 47.1	0.680
LVSVI, mL/m^2	40.9 ± 13.2	41.6 ± 12.9	36.9 ± 12.2	0.043
RV parameters				
RVEF, %	44.9 ± 13.3	40.8 ± 15.9	36.5 ± 14.5*	0.003
RVMI, g/m^2	17.2 (14.5–21.4)	19.0 (15.8–24.0)	19.6 (16.1–24.7)*	0.025
RVRI, g/mL	0.29 (0.25–0.33)	0.29 (0.27–0.34)	0.31 (0.27–0.38)	0.081
RVEDVI, mL/m^2	61.3 ± 19.6	69.1 ± 25.3	68.9 ± 28.4	0.079
RVESVI, mL/m^2	34.9 ± 17.2	42.7 ± 24.1	46.0 ± 28.5*	0.013
RVSVI, mL/m^2	26.5 ± 9.2	26.4 ± 9.8	22.9 ± 8.4*	0.022

The data are presented as the means ± SDs or median (Q1–Q3)

HFrEF: heart failure with reduced ejection fraction; HTN: hypertension; DM: diabetes mellitus; LV: left ventricular; RV: right ventricular; EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; M: mass; I: indexed to BSA; LV/RVRI: left/right ventricular remodeling index

*P less than 0.05 vs. HFrEF controls

§P less than 0.05 vs. HTN-HFrEF (DM–) group

Table 3 Comparison of the LV and RV strain parameters

	HFrEF controls *n* = 77	HTN-HFrEF(DM-) *n* = 97	HTN-HFrEF(DM+) *n* = 75	*P* value
LV parameters				
GRS (%)	10.4 ± 4.2	9.4 ± 4.6	7.9 ± 3.3*	0.001
GCS (%)	-8.5 ± 2.9	-8.1 ± 3.0	-6.8 ± 2.4*§	< 0.001
GLS (%)	-6.9 ± 2.1	-5.7 ± 2.2*	-4.1 ± 1.4*§	< 0.001
RV parameters				
GRS (%)	25.1 ± 7.7	22.4 ± 11.7	18.4 ± 9.2*	< 0.001
GCS (%)	-9.3 ± 4.3	-8.3 ± 3.6	-6.6 ± 3.9*§	< 0.001
GLS (%)	-9.9 ± 3.5	-8.6 ± 3.7*	-6.3 ± 2.8*§	< 0.001

The data are presented as the means ± SDs

The negative signs in GCS and GLS strain values were representative of myocardial shortening during the systolic phase but not the magnitude of the strain values

LV: left ventricular; RV: right ventricular; GRS: global radial strain; GCS: global circumferential strain; GLS: global longitudinal strain

*P less than 0.05 vs. HFrEF controls

§P less than 0.05 vs. HTN-HFrEF (DM–) group

-8.3 ± 3.6% vs. -6.6 ± 3.9%, $P < 0.001$) and LV (-8.5 ± 2.9% vs. -8.6 ± 3.7% vs. -6.8 ± 2.4%, $P < 0.001$) GCS, and lower RV (18.4 ± 9.2% vs. 25.1 ± 7.7%, $P = 0.000$) and LV (7.9 ± 3.3% vs. 10.4 ± 4.2%, $P = 0.001$) GRS than the HFrEF control patients (Table 3).

The detailed global IVS strains of each segment are shown in Fig. 2. The GLS of segments 8, 9 and 14 decreased notably from the HFrEF control group to the HTN-HFrEF (DM-) group to the HTN-HFrEF (DM+) group (all $P < 0.05$). Compared with the HFrEF control and HTN-HFrEF (DM-) groups, the HTN-HFrEF (DM+) group had a lower GRS in segment 2; GCS in segments 8, 9 and 14; and GLS in segments 2 and 3 (all $P < 0.05$), but the values were not significantly different among the three groups in segment 14 GRS ($P = 0.088$) and segment 3 GCS ($P = 0.134$).

Correlations of LV and RV volumetric and functional parameters across groups

In the three HFrEF patient subgroups, LVEF was correlated with LVGRS ($r = 0.70$–0.78), LVGCS (r = -0.77– -0.85), and LVGLS (r = -0.51– -0.57) (all $P < 0.05$), LVEDVI was correlated with LVGCS ($r = 0.25$–0.41) (all $P < 0.05$), and LVESVI was correlated with LVGRS (r = -0.37– -0.50) and LVGCS ($r = 0.45$–0.54) (all $P < 0.05$). RVESVI and RVEF were correlated with RVGRS, RVGCS, and RVGLS (all $P < 0.05$) in all three subgroups, RVEDVI and RVMI were correlated with RVGRS, RVGCS, and RVGLS (all $P < 0.05$) in the hypertensive patient subgroups (Additional file 1).

Associations of RV strains with LV and IVS function in HTN-HFrEF patients

In the HTN-HFrEF patient subgroups, the RVGRS was significantly correlated with LVEF ($r = 0.28$), LVGRS ($r = 0.42$), LVGCS (r=-0.42), and LVGLS (r=-0.50) (all $P < 0.05$). RVGCS and RVGLS were both significantly correlated with LVEF (r=-0.28 and -0.36), LVGRS (r=-0.38 and -0.46), LVGCS ($r = 0.40$ and 0.48), LVGLS ($r = 0.46$ and 0.59) and LVMI ($r = 0.18$ and 0.16) (all $P < 0.05$). In addition, RVEF and all RV global strains were correlated with the IVS GCS and GLS strains of all segments (all $P < 0.05$) (Fig. 3).

Determinants of RV strain parameters

For the HTN-HFrEF patient subgroups, we conducted multivariable linear regression to identify the determinants of impaired RV strains. After adjusting for covariates (age, sex, BMI, heart rate, PP, eGFR, smoking status, TG, TC, HDL, LDL, NT-proBNP, HTN duration, CAD, obesity and AF), DM was found to be independently associated with the RVGCS (β = 0.22, $P = 0.004$) and RVGLS (β = 0.29, $P < 0.001$). When LVEF, LVMI, RVMI, and LV strain were added to the regression analyses, DM and RVMI were independently associated with the RVGCS (β = 0.14 and β = 0.21, $P = 0.048$ and $P = 0.005$) and RVGLS (β = 0.14 and β = 0.18, $P = 0.035$ and $P = 0.006$), the LVGCS was independently associated with the RVGCS (β = 0.27, $P < 0.001$), and the LVGLS was independently associated with the RVGLS (β = 0.46, $P < 0.001$), however,

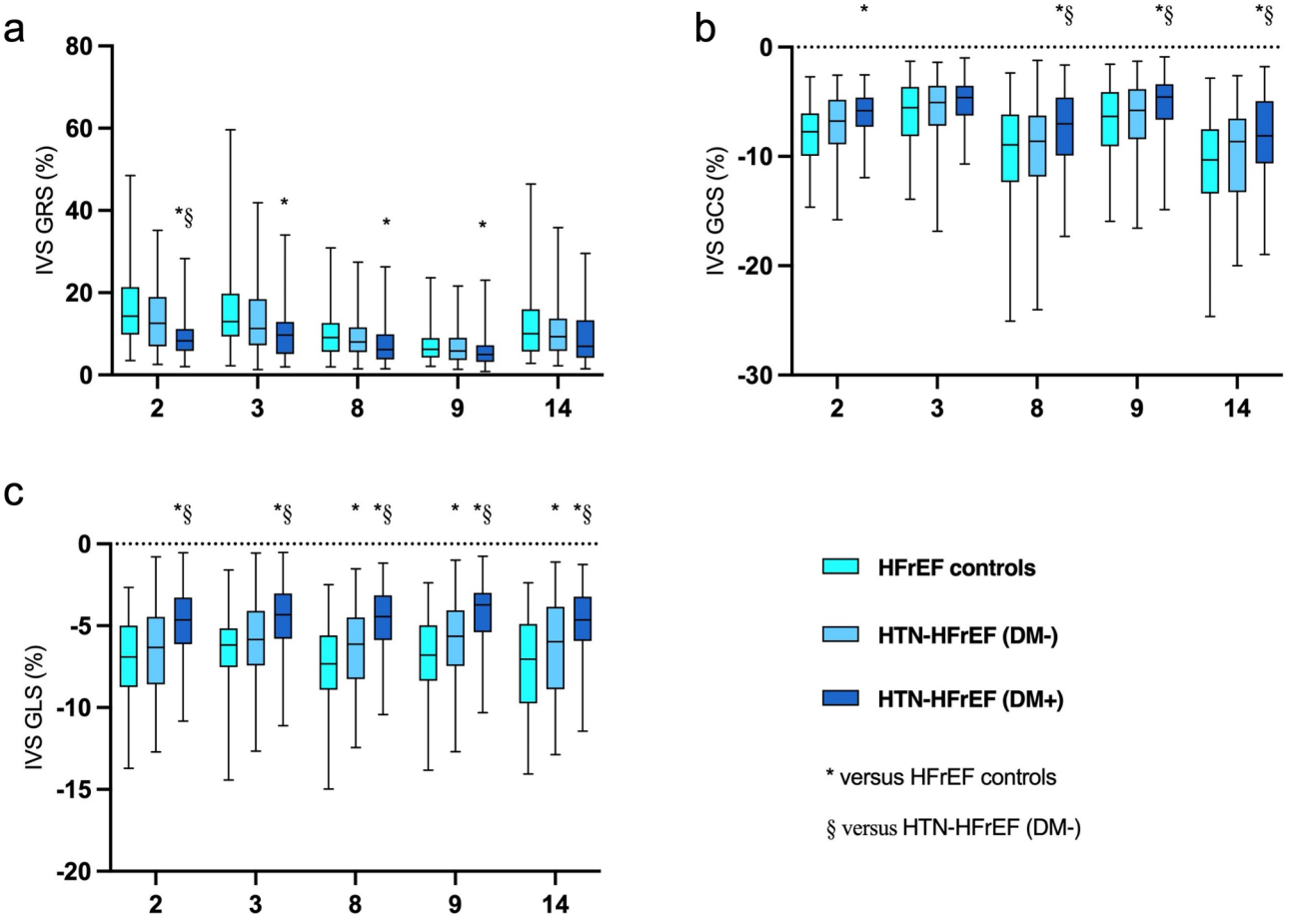

Fig. 2 Comparison of global strains in segments 2, 3, 8, 9 and 14 representing the area of interventricular septum (IVS) among groups. Boxplots represent the median and interquartile range for GRS, GCS and GLS strains of IVS segments. HFrEF: heart failure with reduced ejection fraction; HTN: hypertension; DM: diabetes mellitus; GRS: global radial strain; GCS: global circumferential strain; GLS: global longitudinal strain

LVMI was not significantly associated with both RVGCS and RVGLS (both $P>0.05$) (Table 4).

Direct and indirect mediating effects of DM on RV strains

The direct and indirect effects of DM on RV strains with the mediator LV strain and the same covariates added in multivariable linear regression Model 2 are displayed in Additional file 2. The difference in RVGLS between the hypertensive HFrEF subgroups was directly affected by DM [β=1.00, 95% CI (0.10–1.90)] and partly mediated by LVGLS [β=0.80, 95% CI (0.39–1.31)]. The difference in RVGCS between the hypertensive HFrEF subgroups was directly affected by DM [β=1.10, 95% CI (0.02–2.17)] and partly mediated by the LVGCS [β=0.28, 95% CI (0.01–0.62)] (Table 5).

Clinical outcomes of the study cohort

During a median follow-up of 34.3 (21.5–48.2) months, the primary composite outcomes, which included 38 HF readmissions, 17 all-cause deaths and 2 heart transplantations, occurred in 57 patients. The primary composite events occurred most frequently in the HTN-HFrEF (DM+) group than in the HFrEF control and HTN-HFrEF (DM-) groups (34.7% vs. 15.6% vs. 19.6%, $P=0.012$). By Kaplan-Meier survival analysis, patients in the HTN-HFrEF (DM+) group were more likely to experience adverse outcomes than those in the HFrEF control and HTN-HFrEF (DM-) groups (log-rank $P=0.014$; Fig. 4).

Discussion

In the present study, we used a cardiac MRI feature tracking technique to evaluate the effect of DM on RV structure and global RV myocardial strain in hypertensive HFrEF patients and to investigate the associations of RV strains with LV and IVS function; the mediating effects of LV strain on RV strain through the septum were also evaluated. Our data revealed the following main findings: (1) In hypertensive patients with HFrEF, the RVGLS, LVGLS and IVS GLS were lower than they were in HFrEF control patients, and DM further deteriorated RV GLS and GCS; however, there was no significant difference in the RV remodeling index between the two hypertensive

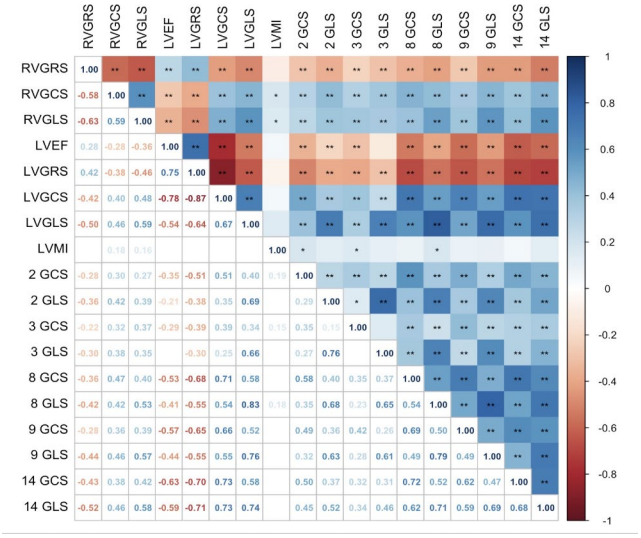

Fig. 3 Heatmaps illustrating the associations between cardiac MRI-derived RV strains with LV and IVS functional parameters in HTN-HFrEF patients. Each cell represents the correlation between the two parameters of the horizontal and vertical axes at that location, and the numbers within the cells indicate the bivariate correlation coefficients. The color shading of each cell corresponds to the direction and magnitude of the correlation coefficient, with red indicating a negative correlation and blue indicating a positive correlation; ** represents P less than 0.01, and * represents P less than 0.05. The 2, 3, 8, 9 and 14 GCS and GLS represent the GCS and GLS in segments 2, 3, 8, 9 and 14 representing the area of interventricular septum. The abbreviations are consistent with those in Tables 2 and 3.

Table 4 Determinants of impaired RV strains in HTN-HFrEF patients

	RVGCS		RVGLS	
	Coefficient (95% CI)	Adjusted R^2	Coefficient (95% CI)	Adjusted R^2
Model 1		0.121		0.169
DM	0.22 (0.56–2.79)*		0.29 (1.08–3.05)*	
Model 2		0.255		0.399
DM	0.14 (0.01–2.15)*		0.14 (0.07–1.86)*	
LV strain	LVGCS: 0.27 (0.18–0.57)*		LVGLS: 0.46 (0.56–1.02)*	
LVMI	-		-	
RVMI	0.21 (0.15–0.82)*		0.18 (0.02–0.12)*	

The abbreviations of DM are shown in Table 1; LVMI, RVMI are shown in Table 2; LVGCS, LVGLS, RVGCS, RVGLS are shown in Table 3

*P value < 0.05; Values are standardized estimate coefficients (B) and 95% confident interval (CI)

Variables with P value < 0.05 were included in the multivariable regression analyses

Model 1: coefficients represent change that was adjusted for age, sex, BMI, heart rate, PP, eGFR, smoking status, TG, TC, HDL, LDL, NT-proBNP[&], HTN duration, CAD, obesity and AF

[&] NT-proBNP is log-transformed before being included in Model 1

Model 2 was adjusted for LVMI, RVMI, LVEF and LV strain in addition to Model 1

Table 5 Mediating effects of DM on the RVGCS and RVGLS with the LV strains as mediators

	RVGCS[a]		RVGLS[a]	
	Direct effect	Indirect effect	Direct effect	Indirect effect
LVGCS	1.10 (0.02–2.17)*	0.28 (0.01–0.62)*	-	-
LVGLS	-		1.00 (0.10–1.90)*	0.80 (0.39–1.31)*

Notes for Table 5:

The abbreviations for LVGCS, LVGLS, RVGCS, and RVGLS are consistent with those in Table 3

[a]Adjusted for covariates added in the multivariable linear regression Model 2 shown in Table 4

*P value < 0.05

subgroups. (2) DM was an independent determinant of impaired RV strains. (3) Global RV strains were correlated with LV and IVS strains, and impaired RV strains were partially mediated by LV strains in hypertensive HFrEF patients.

DM aggravates RV dysfunction in HFrEF patients with comorbid HTN

Similar to the way in which the LV myocardium is damaged, the increased load induced by long-standing HTN also damages the RV myocardium, which is characterized mainly by RV myocardial hypertrophy and reduced systolic and diastolic function [22, 23], and HTN can cause RV remodeling in the absence of lung diseases or pulmonary HTN [22]. Consistent with their findings, our study revealed that hypertensive HFrEF patients with or without DM had decreased RVGLS and IVS GLS, which is a reflection of impaired RV systolic function, and an elevated RVMI compared with those of HFrEF control patients.

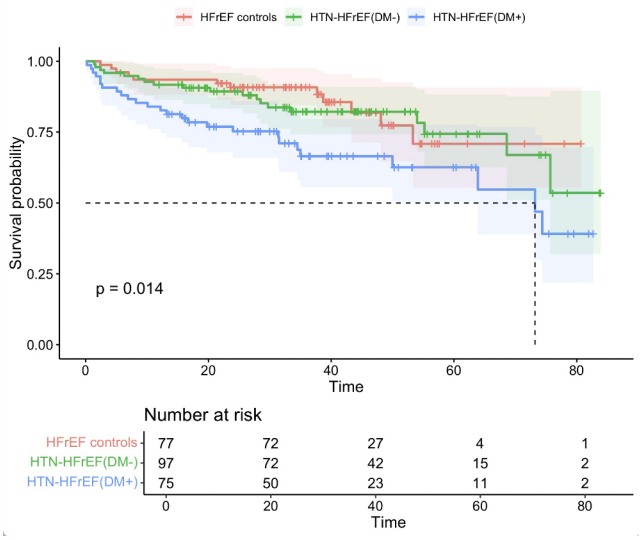

Fig. 4 Survival curves of the study cohort during a median follow-up of 34.3 months

HTN and DM are two common comorbidities of HFrEF, and they often coexist. In HTN-HFrEF patients with coexisting DM, our results revealed that RVGCS and RVGLS were further deteriorated compared with those without. In an animal study, Black MJ. et al. [24] reported a greater degree of myocardial fibrosis in hypertensive rats with concurrent DM, which may partially explain our results. Recently, in a prospective study, Li. et al. [25] also reported biventricular dysfunction and a greater degree of myocardial fibrosis in nonischemic dilated cardiomyopathy patients with type 2 DM than in those without DM in an HF cohort. In contrast to the findings of Li. et al. [16] derived from a population without HF, the damage caused by comorbid DM on global RV strains in HTN patients occurred only in the longitudinal direction. We hypothesized that this difference might be due to the different disease durations, since the RV endothelium is arranged in the longitudinal direction and the epithelium in the circumferential direction, and similar to the process of interstitial fibrosis in the LV [26, 27], the RV dysfunction caused by interstitial fibrosis may evolve from the RV endothelium to the epithelium. Compared with non-HF HTN patients, the patients in this study had a longer disease course and duration, and the fibrosis caused by comorbid DM may involve the epicardial circumferential fibers, causing a decrease in the RVGCS. Notably, there was no significant difference in RVRI among the three groups of patients in this study, suggesting that impairment of RV strain by DM in HTN-HFrEF patients occurs prior to morphological changes, and since RV strain is associated with patient prognosis, early identification of abnormal RV function via strain assessment may be beneficial for risk stratification of HTN-HFrEF patients with DM.

Determinants of impaired LV function in HTN-HFrEF patients

In HTN-HFrEF patients, after adjusting for covariates in the final model of multivariable linear regression, DM was found to be independently associated with impaired RV strains. Currently, studies on the mechanisms by which DM causes RV impairment are limited; although the RV has a unique cellular origin and composition, as well as unique biomechanical properties, DM may contribute to RV impairment through the same pathways that cause LV impairment, such as insulin resistance and oxidative damage [28, 29]. The use of sodium–glucose cotransporter 2 inhibitors (SGLT2is) can reduce the incidence of cardiovascular events and reverse LV remodeling, and they have been defined as the first-line therapy in HF patients with comorbid DM in the relevant guidelines [1]. However, SGLT2i treatment does not significantly improve RV remodeling, which means that DM complicates the treatment of HFrEF patients who experience RV dysfunction [30]. Taken together, concurrent biventricular dysfunction in HTN-HFrEF patients with comorbid DM should be emphasized in clinical practice, and early intervention should be initiated. The RVMI was also found to be independently associated with impaired RV strains in our study. An increased RVM is an adaptation of myocardial hypertrophy, which can be caused by HTN, DM, and pulmonary HTN. Similar to the role of increased LVM in predicting left heart disease prognosis, RVM independently predicts prognosis in patients with pulmonary HTN [31, 32], and cardiac MRI measured RVM may serve as a new marker for assessing clinical progression in postoperative adult patients with tetralogy of Fallot [33].

Ventricular interdependence in HTN-HFrEF patients

RV contractile function is dependent on the interaction between the transverse fibers of the RV free wall and the oblique fibers of the IVS [34]. Approximately 20–40% of RV output is related to LV contraction [35]. As the RV is anatomically linked to the LV through the septum, RV contractile function is related to some extent to ventricular interdependence, i.e., the force transmitted from one ventricle to the other through the myocardium and the septum [34]. Previous studies have revealed that RV dysfunction is related to the occurrence of LV remodeling or dysfunction in patients without HF [16, 36–38]. Our study revealed significant associations of global RV strains with global LV and IVS strains in HTN-HFrEF patients, and LVGCS and LVGLS were independently associated with impaired RV strains, which confirmed ventricular independence in this cohort of patients. In addition, we investigated whether the additive effect of DM on impaired RV strains was mediated by LV strains and found that the RVGCS and RVGLS were partially mediated by LV strains in hypertensive HFrEF patients.

Limitations

There are several limitations of this study that cannot be ignored. First, there might be potential selection bias due to the retrospective and single-center design of the study. Second, the duration of DM is an important reference for myocardial microstructural changes, and in the present study, we did not stratify HTN-HFrEF patients with comorbid DM according to the duration of DM. Finally, myocardial fibrosis assessed by cardiac MRI late gadolinium enhancement or extracellular volume were not evaluated in the present study, it would be interesting to know how DM effect myocardial fibrosis in HTN-HFrEF patients by further studies.

Conclusions

In hypertensive HFrEF patients, comorbid DM may aggravate RV dysfunction and is an independent determinant of impaired RV strain. RV dysfunction is associated with LV and IVS strain injury which may be caused by comorbid DM due to unfavorable ventricular independence, and impaired RV strains are mediated by LV strains. RV dysfunction should be supervised and treated together with LV dysfunction to improve patient prognosis.

Abbreviations

HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
DM	Diabetes mellitus
LV	Left ventricular
RV	Right ventricular
IVS	Interventricular septum
EF	Ejection fraction
EDV	End-diastolic volume
ESV	End-systolic volume
SV	Stroke volume
GRS	Global radial strain
GCS	Global circumferential strain
GLS	Global longitudinal strain

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02472-z.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

Not applicable.

Author contributions

G.Z., K.S., Y.L. and Z.G.Y designed the study. G.Z., R.S. and X.M.L interpreted the data and wrote the manuscript. G.Z., W.F.Y and X.M.L were responsible for collecting and sorting statistical data. R.S., W.F.Y and X.M.L analyzed the data and gave advice on data presentation. H.Y.X., K.S. and Y.K.G revised the manuscript. Z.G.Y supervised the overall study and reviewed the manuscript. All authors reviewed and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Biomedical Research Ethics Committees of our West China hospital. Written informed consent was waived because of the retrospective nature of this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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